REMARKS

IN THE SPECIFICATION

A typographical proofreading correction has been made in the paragraph bridging pages 6-7.

IN THE CLAIMS

Claim 12 has been canceled. Claims 1, 2, 8, 14, 21 and 24 have been amended to point out with greater clarity and particularity the subject matter regarded by the Applicants as their invention and/or to conform to Group I of the Restriction Requirement.

Claims 1, 14 and 24 have been amended to direct the claims to Group I of the March 6, 2007 restriction requirement, that is, to methods wherein the MN/CA9 expression products are MN/CA IX proteins/polypeptides. Applicants respectfully submit that the amendments to Claims 1, 14 and 24 are supported throughout the instant application, for example, the Specification reads at page 6, lines 21-28:

> Preferred assays to be used according to the methods of the invention to detect said MN/CA9 gene expression product in detecting step (a) are those wherein said MN/CA9 gene expression product comprises an MN/CA IX protein or MN/CA IX polypeptide, and said assays are selected from the group consisting of Western blots, enzyme-linked immunosorbent assays, radioimmunoassays, competition immunoassays, dual antibody sandwich assays, immunohistochemical staining assays, agglutination assays, fluorescent immunoassays, and cytofluorometry.

[Emphasis added.]

Claim 1 has been further amended to specify that said MN/CA IX protein or MN/CA IX polypeptide is "specifically bound by the M75 monoclonal antibody that is secreted from the hybridoma VU-M75, which was deposited at the American Type Culture Collection under ATCC No. HB 11128." Support for that amendment can be found in the Specification at least at page 31, lines 9-14, which reads:

> Preferred MN proteins/polypeptides are those proteins and/or polypeptides that have substantial homology with the MN protein shown in Figure 1. For example, such

> substantially homologous MN proteins/polypeptides are those that are reactive with the MN-specific antibodies, preferably the Mab M75 or its equivalent. The VU-M75 hybridoma that secretes the M75 Mab was deposited at the ATCC under HB 11128 on Sep. 17, 1992.

Claim 2 has been amended for greater clarity and particularity, to clarify that it recites a limitation to Claim 1, rather than a result. Claim 2 now reads: "The method of Claim 1 wherein said normal expression of MN/CA IX protein in said tissue indicates that 40% or more of the cells of said tissue express MN/CA IX protein."

Claim 8 has been amended for greater clarity and particularity as suggested by the Examiner, to specify that the sample within the phrase "immunoreactivity score of the sample determined in steps b(1) to b(3) . . ." is the subject vertebrate sample.

Support for the amendment to Claim 21, wherein a method step is provided, can be found in the Specification at least at page 23, lines 1-3, which reads: "In particular, the levels of *CA9* gene expression products can be used to predict clinical outcome and to identify high risk patients in need of adjuvant therapies." [Emphasis added.]

Claim 24 has also been amended as suggested by the Examiner for greater clarity and particularity, to recite: "said tissue loses MN/CA IX expression or expression of MN/CA IX is significantly reduced upon carcinogenesis. . . ."

Applicants respectfully conclude that no new matter has been entered by any of the above amendments.

I. Claim Objections

Claim 2 stands "objected to for failing to further limit the claim from which it depends. Claim 2 appears to recite a result rather than a limitation to the claim from which it depends. Proper correction is required." [Instant Office Action, at page 3.] For greater clarity and particularity, Claim 2 has been amended to recite "wherein said normal expression of MN/CA IX protein in said tissue indicates that 40% or more of the cells of said tissue express MN/CA IX protein." Applicants respectfully submit that the "tissue" of Claim 2 as amended now clearly refers to the type of normal tissue, not

the tissue sample that is being tested according to the methods of the invention, and therefore does not recite a result.

Claim 24 is objected to for reciting in step (b) a "detecting" step, rather than a "determining" step. Claim 24 has consequently been amended as helpfully suggested by the Examiner at page 3 of the Office Action.

II. 35 USC 101 Rejection

Claim 21 stands rejected under 35 USC 101 "because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process. . . ." [Office Action, at page 4.] Applicants respectfully submit that, as discussed above, the amendment to Claim 21 provides a method step for Claim 21, and therefore overcomes the instant rejection.

III. 35 USC 112, Second Paragraph Rejections

Claims 1-12, 14, 16 and 18-24 stand rejected under 35 USC 112, second paragraph, "as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." [Office Action, at page 4.] Applicants respectfully traverse, submitting that the amendments to the claims and the following arguments overcome the instant rejection, for which each aspect is discussed separately below.

Claim 1 and Dependent Claims 2-12, 14, 16 and 18-23

Claim 1 and dependent Claims 2-12, 14, 16 and 18-23 are rejected because the "poorer prognosis" recited in Claim 1 is not specified. Applicants respectfully argue that the term "poorer prognosis" is conventional in the prognostic art related to cancer, and restricting Claim 1 to a type or types of poorer prognosis would unduly limit the protection of the invention. Applicants respectfully point out that a "specification is directed to those skilled in the art and need not teach or point out in detail that which is well-known in the art." [In re Myers, 161 USPQ 668, 671 (CCPA 1969.] Claims are to be read in light of the specification, which describes exemplary and preferred prognoses of "shortened survival, increased risk of recurrence of said

preneoplastic/neoplastic disease, or . . . diminished or refractory response to treatment." [Specification, at page 9, lines 22-25.]

Claim 8

Claim 8 is rejected as indefinite for

> reciting "weak staining", "moderate staining", and "strong staining". . . . This renders the claim indefinite because the terms "weak, "moderate", and "strong" staining are not defined by the claim, the specification does not provide a standard for ascertaining the requisite degrees, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

[Office Action, paragraph bridging pages 4-5.] Applicants respectfully disagree, countering that the terms "weak", "moderate", and "strong" staining are conventional and well-understood by those of skill in the art of immunohistochemistry, as part of a semiquantitative grading system termed "an immunoreactive score" ("IRS," usually based on staining intensity and a percentage of positive cells).

Such semiquantitative analyses, although based on subjective scoring, is standard in the immunohistochemical art and has been confirmed as a reliable method. For example, comparative studies have shown high correlations between subjective IRS scoring and objective computer-assisted image analysis [e.g., estrogen receptor expression in breast cancer reported in Kohlberger et al., Anticancer Res., 19(3B): 2189-2193 (1999); and metallothionein expression in liver-biopsies in Alscher et al., Exp. Toxicol. Pathol., 54(3): 245-253 (2002).]. Copies of the abstracts of Kohlberger et al. (1999) and Alscher et al. (2002) are attached to this response.

The following statements found in the attached abstracts of Kohlberger et al. and Alscher et al. support the reliability of the use of semi-quantitative IRS scoring in immunohistochemistry:

> Eighty formalin-fixed, paraffin-embedded and immunohistochemically stained breast cancer specimens were assessed for estrogen receptor expression by true color computer-assisted image analysis and by conventional light microscopy scoring according to Remmele (immunoreactive score (IRS) = staining intensity (SI) x percentage of positive cells (PP)). The results of both

> methods were correlated. RESULTS: Mean optical density (MOD) and subjective scoring of SI as well as stained nuclear area vs. total nuclear area and subjective scoring of stained cells (PP) showed a high correlation. . . . [O]ur results confirm the correlation of semiquantitative hormone receptor scoring and quantitative computer-assisted image analysis.

[Abstract, Kohlberger et al. (1999); emphasis added.]

> We investigated paraffin embedded liver biopsies from 170 patients and 13 control biopsies from cases of sudden death. Tissue was stained with a primary antibody against MT and a peroxidase technique was used to make results visible. A grading was performed using an immunoreactive score (IRS from 0-24) and by computer-aided measurement of the optical density (OD) of the stained tissue slides. Patients . . . showed marked increases in MT compared to the controls.
> . . . Results by OD confirmed the findings.

[Abstract, Kohlberger et al. (2002); emphasis added.]

A "specification is directed to those skilled in the art and need not teach or point out in detail that which is well-known in the art." [In re Myers, 161 USPQ 668, 671 (CCPA 1969); see also, G.E. Col. v. Brenner, 159 USPQ 335 (CAFC 1968).] As the Federal Circuit stated in Spectra-Physics, Inc. v. Coherent, Inc., 3 USPQ2d 1737, 1743 (Fed. Cir. 1987): "A patent need not teach, and preferably omits, what is well known in the art." [Emphasis added.]

Further, Applicants respectfully direct the Examiner's attention to case law concerning the use of words of degree (relational terms), such as, for example, Andrews Corp. v. Gabriel Electronics Inc., 847 F.2d 819, 821-22, 6 USPQ2d 2010, 2012-2013 (Fed. Cir. 1988). The Federal Circuit stated in that case at pages 2012-2013 as follows:

> [T]erms in the claims such as "approach each other", "close to", "substantially equal", and "closely approximate", . . . are ubiquitous in patent claims. Such usages, when serving reasonably to describe the claimed subject matter to those of skill in the field of the invention, and to distinguish the claimed subject matter from the prior art, have been accepted in patent examination and upheld by the courts. As this court put it in Rosemount, Inc. v.

Beckman Instruments Inc., 727 F.2d 1540, 1546-47, 221 USPQ 1, 7 (Fed. Cir. 1984):

> Beckman attacks the claims as indefinite, primarily because "close proximity" is not specifically or precisely defined. . . . **"to accept Beckman's contention would turn the construction of a patent into a mere semantic quibble that serves no useful purpose."**
>
> In Rosemount the district court found that "'close proximity' is as precise as the subject matter permits". Id In Seattle Box Co. v. Industrial Crating & Packaging, . . . 221 USPQ 568, 573-74 (Fed. Cir. 1984). . . . the court remarked that "substantially equal" is a term of degree, and that its acceptability depends on "whether one of ordinary skill in the art would understand what is claimed . . . in light of the specification", even if experimentation may be needed.
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> . . . See also Hybritech Inc. v. Monoclonal Antibodies, Inc., . . . 231 USPQ 81, 95 (Fed. Cir. 1986) ("**the claims, read in light of the specification, reasonably apprise those skilled in the art and are as precise as the subject matter permits**. As a matter of law, no court can demand more"), ...

[Emphasis added.]

[See also, ZMI Corp. v. Cardiac Resuscitator Corp., 2 USPQ2d 1985, 1989 (D. Ore. 1987), *rev'd. in part, vacated in part and remanded,* 6 USPQ2d 1557 (Fed. Cir. 1988) ("The use of terms like `constant' and `low' does not render a patent indefinite unless a person of ordinary skill in the art would not be able to determine from the claims what would be infringing and what would not be infringing.").]

Analogously to the phrases discussed in Andrew-Corp. and Rosemount, supra, such as, "substantially equal," "closely appropriate," and "close proximity" which were found by the Federal Circuit to be "as precise as the subject matter permits. . . ." Applicants respectfully submit that the phrases "weak staining," "moderate staining," and strong staining" are phrases well known in the immunohistochemical staining art and "in light of the specification, reasonably apprise those skilled in the art and are as precise as the subject matter permits." [Quote above from Hybritech.] Applicants

respectfully conclude that Claim 8 has sufficient definiteness with respect to the phrases "weak staining," "moderate staining," and "strong staining" which phrases are "as precise as the subject matter permits." [Id.]

Claim 8 has also been rejected for reciting "wherein if the immunoreactivity score of **the sample** determined in steps b(1) to b(3) is above the average immunoreactivity score of said comparable samples. . . ." [Office Action, at page 5.] Claim 8 has been amended as suggested by the Examiner, to read instead: "wherein if the immunoreactivity score of the subject vertebrate sample determined in steps b(1) to b(3) is above the average immunoreactivity score of said comparable samples. . . ." Applicants respectfully conclude that that amendment overcomes the subject rejection.

Claim 21

Claim 21 stands rejected as indefinite for reciting a use without any active, positive steps. As discussed above in relation to the 35 USC 101 rejection, Claim 21 has been amended to recite an active method step. Applicants respectfully conclude that that amendment overcomes the subject rejection.

Claim 24

Claim 24 stands rejected for reciting "said tissue loses or expresses MN/CA IX at a significantly reduced level upon carcinogenesis. . . ." [Office Action, at page 6]. Applicants respectfully point out that Claim 24 has been amended as recommended by the Examiner, to recite instead: "said tissue loses **MN/CA IX expression** or **expression of** MN/CA IX **is** significantly reduced upon carcinogenesis . . . ," and that that amendment should overcome the subjection rejection.

Claim 24 is also rejected for reciting "the level that said MN/CA9 gene expression product is normally expressed in said tissue, **when said tissue is unaffected by said disease . . . ,**" for the reason that "[i]t is unclear how a tissue sample from the invasion front of a preneoplastic/neoplastic disease can comprise a tissue unaffected by a preneoplastic/neoplastic disease." [Office Action, at page 6.] Applicants respectfully submit that the Examiner is mistaken: what is being compared

is the level of MN/CA IX protein/polypeptide "in the invasion front sample as compared to the level . . ." of MN/CA IX protein/polypeptide "normally expressed in said tissue, when said tissue is unaffected by said disease. . . ." [Claim 24 (b) as amended above.] The antecedent for "said tissue" would necessarily be "**a tissue**," not "**a tissue sample**." The antecedent for "said tissue" in the cited phrase of Claim 24 is "a tissue in which 40% or more of the cells normally express MN/CA IX protein . . . ," and not "a tissue **sample** from the invasion front of said preneoplastic/neoplastic disease. . . ."

Conclusion Regarding 35 USC 112, Second Paragraph Rejection

Applicants respectfully conclude that the claim amendments and above explanations address the subject 35 USC § 112, second paragraph rejection and, request that the Examiner reconsider and withdraw the instant rejection

IV. 35 USC 112, First Paragraph Rejection – Written Description

Claims 1-12, 14, 16 and 18-24 stand rejected under 35 USC 112, first paragraph, as "failing to comply with the written description requirement." [Office Action, at page 6.] Applicants respectfully traverse this rejection, first respectfully pointing out that the subject claims are original claims, and as pointed out by the Manual of Patent Examining Procedures (MPEP) § 2163 (II)(A): "[R]ejection of an original claim for lack of written description should be rare." [Emphasis added.]

Numerous cases hold that an "original claim," that is, one contained in the specification when it is filed, complies with the Section 112 invention description requirement. [See, for example, In re Koller, 204 USPQ 702 (CCPA 1980); Union Oil Co. of California v. Atlantic Richfield Co., 54 USPQ2d 1227 (Fed. Cir. 2000).] For example, the Court of Customs and Patent Appeals (CCPA)[1] in In re Smith, 481 F.2d

1. The CCPA is a predecessor court to the Court of Appeals for the Federal Circuit. In the Federal Circuit's first reported opinion, South Corp. v. United States, 215 USPQ 657 (Fed. Cir. 1982), the Federal Circuit adopted as binding precedent "the holdings of our predecessor courts, the United States Court of Claims and the United States Court of Customs and Patent Appeals [CCPA]. . . ."

910, 178 USPQ 620 at 623 (CCPA 1973) stated: "Where the claim is an original claim, the underlying concept of insuring disclosure as of the filing date is satisfied, and the description requirement has likewise been held to be satisfied."

The Manual of Patent Examining Procedure in Section 2163(I)- (II) states:

> There is a strong presumption that an adequate written description of the claimed invention is present when the application is filed. *In re Wertheim*, 541 F.2d 257, 263, 191 USPQ 90, 97 (CCPA 1976) ("we are of the opinion that the PTO has the initial burden of presenting evidence or reasons why persons skilled in the art would not recognize in the disclosure a description of the invention defined by the claims").
>
> . . . .
>
> Consequently, rejection of an original claim for lack of written description should be rare.

[Emphasis added.]

The PTO's Written Description Guidelines [Fed. Reg., Vol. 66, No. 4 (Jan. 5, 2001)] similarly indicate that there is a "strong presumption that an adequate written description of the claimed invention is present when the application is filed, consistent with In re Wertheim, supra.

> The Guidelines emphasize that the burden of proof is on the **examiner to establish that a description as filed is not adequate and require the examiner to introduce sufficient evidence or technical reasoning to shift the burden of going forward with contrary evidence to the applicant**.

[*Id.* at page 1100, col. 3; emphasis added.] Applicants respectfully submit that the Examiner has not introduced sufficient evidence to shift the initial burden of proof to the Applicants, but if **hypothetically** that burden had been shifted, the Applicants demonstrate below that that burden would be overturned.

The Office Action argues that "[t]he instant specification fails to provide sufficient descriptive information, such as definitive structural or functional features that are common to the genera . . ." [Office Action, top of page 9], wherein "the

genera" refer to (1) a genus of samples comprising preneoplastic/neoplastic tissue, which tissue normally expresses MN/CA IX protein, but loses or has significantly reduced MN/CA IX expression upon carcinogenesis; (2) a genus of MN/CA IX protein variants; and (3) a genus of tissue samples from the invasion front of preneoplastic/neoplastic disease. [Office Action, top of page 7.] The Office Action then mistakenly (as will be shown below) states at page 8 that

> the written description in this case only sets forth tissue samples from gastric cancers as tissue samples from the invasion front of preneoplastic/neoplastic disease afflicting a subject vertebrate, wherein said disease affects a tissue in which 40% or more of the cells normally express MN/CA IX protein, but said tissue loses MN/CA IX expression or expression of MN/CA IX is significantly reduced upon carcinogenesis. . . .
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> . . . [T]he state of the art is such that it is unclear which cancers, other than gastric cancers, result in a decrease in MN/CA IX expression upon carcinogenesis.

The Office Action erroneously concludes that "one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe and enable the genera as broadly claimed." [Office Action, middle of page 9.]

Applicants respectfully traverse the subject rejection making the following points and correcting mistakes that underlie the rejection:

1. As pointed out above, the subject claims are original claims, and the erroneous rejection has not met the initial burden that rests with the Examiner to present "evidence or reasons why persons skilled in the art would not recognize in the disclosure a description of the invention defined by the claims." [MPEP § 2163(I)-(II), supra.] The Applicants then need not go forward with contrary evidence, as pointed out by the PTO's Written Description Guidelines, supra.

2. The PTO's Written Description Guidelines indicate that "there may be situations where one species adequately supports a genus."

3. Applicants respectfully show that conventional knowledge in the art as recited in the Specification clearly teaches which preneoplastic/ neoplastic diseases result in a decrease in MN/CA IX expression upon carcinogenesis.

4. Applicants respectfully show that the Examiner is mistaken as to the disclosure being limited to a description of "gastric cancer samples" and "invasion front samples."

5. Applicants respectfully point out that the nucleotide sequences of Claim 1, subsection (2) are those that are "substantially complementary" to the complement of SEQ IS NO: 1's coding region, and that Claim 1 as amended specifies a further common feature of the genus of MN/CA IX proteins/polypeptides in said samples, that is, those that are "**specifically bound by the M75 monoclonal antibody that is secreted from the hybridoma VU-M75 which was deposted at the American Type Culture Collection under ATCC No. HB 11128."** [Claim 1, last amendment.]

6. The instant invention is a pioneering invention, and the case law is clear that pioneering inventions are entitled to broad claim coverage.

7. The Office Action is further erroneous in its citation of case law that is inapplicable and inapposite to the circumstances of the instantly claimed methods.

Applicants then respectfully conclude that for the reasons cited above and elaborated below, the "strong presumption" of adequate written description [PTO's Written Description Guidelines, supra] that the original pending claims have remains.

Written Description Requirement for a Genus

Applicants respectfully refer to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement [Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001] ("Guidelines"). The Guidelines support that there is adequate written description in the specification for the claimed genera of (1) preneoplastic/neoplastic diseases; (2) MN/CA IX proteins/polypeptides; and (3) types of tissue samples:

> The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species . . .by disclosure of relevant, identifying characteristic, i.e., structure or other physical and/or chemical properties, . . . sufficient to show the applicant was in possession of the claimed genus. . . . **[T]here may be situations where one species adequately supports a genus**. What constitutes a 'representative number' is an inverse function of the skill and knowledge in the art. Satisfactory disclosure of a "representative number" depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed. . . . **Description of a representative number of species does not require the description to be of such specificity that it would provide individual support for each species that the genus embraces**.

[Guidelines, page 1106, 3rd column; emphasis added.] Applicants will discuss below how the specification supports each of the genera represented by individual species.

Genus of Preneoplastic/Neoplastic Diseases

In arguing undue breadth of the claims, the Examiner contends that the specification only discloses gastric cancer tissue samples [Office Action, at page 7], and that "the state of the art is such that it is unclear which cancers, other than gastric cancers, result in a decrease in MN/CA IX expression upon carcinogenesis." Applicants respectfully disagree, submitting that conventional art referenced in the specification clearly teaches which preneoplastic/neoplastic diseases result in a decrease in MN/CA IX expression upon carcinogenesis.

The Specification in at least two passages [at page 3, line 31 to page 4, line 1; and at page 24, lines 13-16] refers to four articles which describe the cancers that are the subject of the invention.[2] Those four articles identify those tissues in which MN/CA IX is normally expressed (Claim 3) and elucidate that the distribution of MN/CA IX expression in preneoplastic/neoplastic tissues is usually the inverse of that found in normal tissues. For example, Pastorekova and Zavada 2004 [Cancer Therapy, 2: 245-262 (2004)] summarize the findings, explaining that the CA IX expression pattern in cancer tissues is almost perfectly **complementary** to that found in normal tissues:

> CA IX has a distinctive expression pattern: it is naturally expressed in few normal tissues, but its ectopic expression is induced in a wide spectrum of human tumors (Figure 3).
>
> The most abundant expression of CA IX was found in the normal mucosa of the stomach and gallbladder (Pastorekova et al, 1997). Lower levels are expressed in the intestinal epithelium, where it is confined to the cryptal areas composed of cells with high proliferation capacity (Saarnio et al, 1998a). . . . Other normal tissues that display weak expression of CA IX include epithelia of pancreatic ducts, male reproductive organs and lining cells of body cavity (Kivela et al, 2000; Karhumaa et al, 2001; Ivanov et al, 2001).
>
> **Almost perfectly complementary pattern can be seen when looking at the distribution of CA IX in the cancer tissues**. CA IX is ectopically expressed at relatively high levels and with a high prevalence in tumors, whose normal counterparts do not contain this protein. . . . **The opposite expression is evident also in tissues with high natural CA IX expression, such as stomach and gallbladder, which lose or reduce CA IX upon conversion to carcinomas (Saarnio et al, 2001; Leppilampi et al, 2003). . . .**

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2. Those four references are: Pastorekova and Zavada, Cancer Therapy, 2: 245-262 (2004); Pastorekova et al., Gastroenterology, 112: 398-408 (1997); Leppilampi et al., World J Gastroenterol, 9: 1398-1403 (2003); and Saarnio et al., J Hepatol, 35: 643-649 (2001).

[Pastorekova and Zavada 2004, at page 248.] Applicants respectfully submit that the genus of preneoplastic/neoplstic diseases that are the subject of the instantly claimed methods are well known in the art and adequately described.

Genus of Tissue Samples

At page 8, the Office Action states that

> the written description in this case only sets forth tissue samples from gastric cancers as tissue samples from the invasion front of preneoplastic/neoplastic disease afflicting a subject vertebrate, wherein said disease affects a tissue in which 40% or more of the cells normally express MN/CA IX protein, but said tissue loses MN/CA IX expression or expression of MN/CA IX is significantly reduced upon carcinogenesis (see Examples 2 and 3, in particular).

[Emphasis added.] Applicants respectfully submit that the Examiner is mistaken. The cancer samples in Example 2 are only identified as "gastric cancer" samples, not specifically as "invasion front" gastric cancer samples: "Tumor samples were obtained from 18 patients with gastric cancer. . . ." [Example 2, at page 39, lines 14-15.] In Example 3, although MN/CA IX expression in patient immunohistochemical samples is described as being "very prominent at the site of infiltration of the muscularis propria . . . ," indicating that at least one of the samples contains an invasion front, it can most certainly not be inferred that all of the gastric samples contain an invasion front, nor are the number of gastric samples containing an invasion front specified. [Specification, at page 40, lines 13-17.]

Also, in the Materials and Methods section of the Specification, the samples are described as "[t]umorous and corresponding non-tumorous paraffin embedded tissue specimens from 59 patients. . . . For molecular analyses gastric cancer and corresponding non-lesional tissue were obtained immediately after surgery from 18 patients with gastric cancer. . . ." [Specification, at page 34, line 32 to page 35, line 6.] Applicants then respectfully point out that the written description is not limited to a description of invasion front cancer samples, but instead encompasses the genus of all preneoplastic/neoplastic tissue samples from cancers which are known in the art to have decreased MN/CA IX expression upon carcinogenesis.

Genus of MN/CA IX Proteins/Polypeptides

The Examiner argues at page 7 that "the written description only sets forth MN/CA IX proteins encoded by the polynucleotide sequence set-forth as SEQ ID NO:1 and polynucleotide sequences that only differ from SEQ ID NO:1 due to the degeneracy of the genetic code." Applicants first respectfully point out that it is conventional knowledge in the art that only very closely related nucleotide sequences having a homology of at least 80-90% would hybridize to each other under stringent conditions, as required by subsection (b) of Claim 1. The Specification points out that such nucleotide sequences are "substantially complementary to each other, if they hybridize to each other under stringent hybridization conditions." [Specification at page 32, lines 8-13.]

The Specification states at page 31, lines 5-14:

> The phrase "MN proteins and/or polypeptides" (MN proteins/polypeptides) is herein defined to mean proteins and/or polypeptides encoded by an MN gene or fragments thereof. An exemplary and preferred MN protein according to this invention has the deduced amino acid sequence shown in Figure 1. Preferred MN proteins/polypeptides are those proteins and/or polypeptides that have substantial homology with the MN protein shown in Figure 1. For example, such substantially homologous MN proteins/polypeptides are those that are reactive with the MN-specific antibodies, preferably the Mab M75 or its equivalent. The VU-M75 hybridoma that secretes the M75 Mab was deposited at the ATCC under HB 11128 on Sep. 17, 1992.

Applicants respectfully point out that Claim 1 has been explicitly amended now to encompass such MN/CA IX proteins/polypeptides that "have substantial homology with the MN protein shown in Figure 1 . . ." [id.] by describing the MN/CA IX protein/polypeptide of Claim 1, as that that "is specifically bound by the M75 monoclonal antibody that is secreted from the hybridoma VU-M75, which was deposited at the American Type Culture Collection under ATCC No. HB 11128." Applicants respectfully submit that the genus of MN/CA IX protein/polypeptide variants is now described not only in terms of being encoded by substantially complementary

nucleotide sequences to the complement of SEQ ID NO: 1's coding region, but also in terms of specific binding by the M75 Mab -- "common attributes or features of the elements possessed by members of the genus in view of the species disclosed. . . ." [Guidelines, supra.] One of skill in the art would readily recognize the genus of MN/CA IX proteins/polypeptides of Claim 1.

Pioneering Inventions

The case law is clear that pioneer inventions are entitled to broad claim coverage.[3] The purpose recited in the U.S. Constitution for granting patents is "to promote the progress of science and the useful arts by securing for limited times to . . . inventors the exclusive right to their respective . . . discoveries." Applicants respectfully submit that the goal of the Constitution quoted above would not be served by refusing pioneer inventors claims to their new contribution to cancer prognosis.

The Court of Customs and Patent Appeals (CCPA), predecessor court to the Federal Circuit,[4] stated in In re Goffe, 191 USPQ 429 at 431 (CCPA 1976):

> [T]o provide effective incentives, claims must adequately protect inventors. To demand that the first to disclose shall limit his claims to what he has found will work. . . . would not serve the constitutional purpose of promoting progress in the useful arts.

The CCPA further pointed out in In re Hogan and Banks, 194 USPQ 527 at 537 (CCPA 1977):

> As pioneers, . . . they would deserve broad claims to the broad concept. What were once referred to as 'basic inventions' have led to 'basic patents,' which amounted to real incentives, not only to invention and its disclosure, but to its prompt, early disclosure. . . .

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3. A basic patent on a pioneering invention is entitled to be interpreted broadly. Texas Instruments, Inc. v. United States ITC, 231 USPQ 833 (Fed. Cir. 1986).

4. The holdings of the CCPA were adopted as precedent by the Federal Circuit in South Corp. v. United States, 215 USPQ 657 (Fed. Cir. 1982).

> . . . To demand such restriction is merely to state a policy against broad protection for pioneer inventions, a policy both shortsighted and unsound from the standpoint of promoting progress in the useful arts, the constitutional purpose of the patent laws.

In In re Fisher, 166 USPQ 28 at 24 (CCPA 1970), the CCPA considered it "apparent" that a pioneering invention should be able to dominate the future patentable inventions of others where those inventions were based in some way on his/her teachings, that is, where "the improvement was made possible by his work." *Previously, it was unknown whether MN/CA IX expression patterns in preneoplastic/neoplastic tissues, which tissues normally express MN/CA IX but lose expression upon carcinogenesis, could be used for prognosis. The recognition by the Applicants that MN/CA IX expression can be used for prognosis in those preneoplastic/neoplastic tissues that normally express MN/CA IX, but lose expression upon carcinogenesis, provides a benefit to the public as another option for cancer prognosis, and only relates to a limited number of tissues.*

Inapplicability of Case Law Cited

Applicants respectfully distinguish the cases cited at pages 8-10 of the Office Action from the circumstances of the claimed inventive methods in the following paragraphs. Applicants respectfully point out how all the cited cases are inapplicable and inapposite to the subject circumstances and first respectfully note the **commonality** of all of the cases but the University of Rochester v. G.D. Searle Co., 69 USPQ2d 1886 (Fed. Cir. 2004), being inapposite to the instantly claimed methods, in that they concern composition of matter claims to DNA sequences that each encode a human protein, wherein the DNA sequence (gene) had not been yet isolated. In contrast, the instant claims are method claims that are detecting known MN/CA IX proteins/polypeptides that are specifically bound by a known M75 Mab secreted by an ATCC-deposited hybridoma (identified by ATCC No. HB 11128).

Although University of Rochester v. G.D. Searle Co. (id.) concerns methods rather than compositions of matter related to an isolated DNA sequence, it is also misapplied. The claims in the Rochester case were directed to methods of using

non-steroidal compounds to inhibit selectively the activity of the PGHS-2 gene product in humans, wherein the inhibitory ability of the non-steroidal compounds was determined by a specific screening method. The Rochester patent neither disclosed any such compound nor provided any suggestion as to how such a compound could be made or otherwise obtained other than by trial-and-error research, and the claims were found to be invalid for lack of written description. Such claims are far removed from those of the instant method claims which concern the MN/CA IX protein, the amino sequence for which is well known (shown in Figure 1) and substantially homologous MN/CA IX proteins/polypeptides that are specifically bound by a known M75 Mab secreted from an ATCC-deposited hybridoma.

The Office Actions' citation at page 8 to University of California v. Eli Lilly and Co., 43 USPQ2d 1398 at 1406 (Fed. Cir. 1997) refers to a "description of a genus of cDNAs. . . ." In distinction from the Eli Lilly case, the instant claims are to methods not to compositions of matter, and are methods involving a known and isolated cDNA sequence (SEQ ID NO: 1) and DNA sequences that hybridize to the complement of that DNA sequence under standard stringent hybridization conditions and that encode MN/CA IX proteins/polypeptides that are specifically bound by the known M75 Mab.

The "genetic material" found to lack written description in Eli Lilly was the human insulin gene for which the native DNA sequence was **not** provided. The Eli Lilly case is further clearly distinguishable from the instant application in that the involved U.C. patent claims, **as compositions of matter**, recombinant plasmids with cDNA encoding for (1) rat insulin, (2) human insulin, and (3) vertebrate and mammalian insulin. However, the UC inventors had only discovered the sequence for proinsulin (PI) and preproinsulin (PPI) **rat** insulin.

At page 10 of the Office Action, the Examiner cites Fiers v. Revel, 25 USPQ 2d 1601 at 1606 (CAFC 1993) as applicable to the instant claims: "Adequate written description requires more than a mere statement that it is part of the invention and a reference to a potential method of isolating it." However, in Fiers v. Revel, the claim in question did not describe a DNA sequence, but claimed "[t]he DNA coding for a polypeptide having interferon activity insertable in a vector, such as plasmid PBR-322, and having up to 900-1000 nucleotides." Applicants respectfully submit that Fiers v. Revel, in which the claim

only had functional language, does not apply to the instant claims, which do describe an isolated DNA sequence.

Similarly, Applicants respectfully submit that the Amgen case cited by the Examiner at page 10 of the Office Action [Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016 (Fed. Cir. 1991)] is not relevant to the instant claims. In Amgen, as in Fiers v. Revel, the claim in controversy is a composition of matter claim to a DNA sequence that encodes a human protein, wherein the inventor (Fritsch) had not isolated any DNA sequence but only had a potential method for isolating it. The Federal Circuit held in Amgen v. Chugai that conception of an invention does not occur by disclosing a method for obtaining the gene without actually isolating the gene. Again, Applicants respectfully point out that they had possession of the DNA sequence of the MN gene, and are only seeking adequate protection of the claimed inventive methods from would-be infringers.

The Office Action at page 10 refers to Fiddes v. Baird, 30 USPQ2d 1481 (Bd. Pat. App. & Int'f 1993) as concerning

> claims directed to mammalian FGF's . . . [as being] found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence.

However, in Fiddes v. Baird, the applicant Baird was claiming a recombinant DNA molecule that encodes "mammalian" fibroblast growth factor (FGF) wherein the specification disclosed only a **146 amino acid sequence for bovine pituitary FGF but no sequence for the native DNA,** that is, in Fiddes v. Baird, the specification provided no native DNA sequence, bovine or otherwise. The Board in Fiddes v. Baird at pages 1483-1484 relied upon In re Bell, 26 USPQ2d 1529 (Fed. Cir. 1993) for the holding that the

> knowledge of the amino acid sequence of a protein coupled with the established relationship in the genetic code between a nucleic acid and the protein it encodes would not establish possession of the gene encoding that protein . . .
>
> . . . .
>
> Turning to Baird's description of the DNA sequence encoding FGF, we note that he did not postulate the

> correct sequence for the naturally occurring gene but rather a **theoretical DNA sequence for the bovine pituitary FGF out of the myriad possibilities. . . . Thus, Baird was not in possession of the naturally occurring gene for bovine pituitary FGF or any other gene for any mammalian FGF** at the time of filing of the . . . **application.**

[Emphasis added.]

Then, in Fiddes v. Baird, the applicant did not have possession of or a single member of the claimed genus of DNA sequences encoding mammalian FGFs. In contrast, the instant application provides the DNA sequence that encodes the MN/CA IX protein of Figure 1. Fiddes v. Baird is claiming a recombinant DNA that had not been isolated, whereas the instant claims are method claims that relate to a known DNA sequence encoding a known MN/CA IX protein. As pointed out in detail above, the genus of MN/CA IX proteins/polypeptides to which the claimed methods relate have a common feature in being bound by the known M75 Mab accessible from the ATCC.

Applicants respectfully conclude for the reasons detailed above that all of the cases cited in the Office Action are inapposite and inapplicable to the circumstances of the instantly claimed inventive methods.

Written Description Conclusion

Applicants respectfully conclude that the Office Action has not met the PTO's "initial burden of proof of presenting evidence or reasons why persons skilled in the art would not recognize in the disclosure a description of the invention defined by the claims . . ." [MPEP § 2163(I)-(II), supra], and that even if ***hypothetically*** that burden had been shifted to the Applicants, that the Applicants have shown by the above remarks, evidence and argument that the "strong presumption that an adequate description of the claimed invention is present when the application is filed . . ." [PTO's Written Description Guidelines, supra] is warranted in regard to the pending claims. Applicants respectfully remind the Examiner that the "rejection of an original claim for lack of written description should be rare .. ."[id.] and request that the subject rejection be reconsidered and withdrawn.

V. 35 USC 112, First Paragraph Rejection – Lack of Enablement

Claims 1-12, 14, 16 and 18-24 stand rejected under 35 USC 112, first paragraph, as "[t]he specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims." [Office Action, at page 11.] More specifically, the Examiner argues that the specification lacks enablement because

> the specification, while being enabling for a method which is prognostic for a patient with gastric cancer. . . . does not reasonably provide enablement for a method which is prognostic for every preneoplastic/neoplastic disease afflicting a subject vertebrate, wherein said disease affects a tissue, which tissue normally expresses MN/CA IX protein, but loses or has significantly reduced MN/CA IX expression upon carcinogenesis, comprising (a) detecting MN/CA 9 polypeptide in just any sample comprising preneoplastic/neoplastic tissue . . . , (b) quantitating the level of said MN/CA9 polypeptide in said sample,(c) comparing the level of MN/CA9 polypeptide of step (b) to the average level of MN/CA9 polypeptide in just any "comparable" samples taken from vertebrates afflicted by the same preneoplastic/neoplastic disease as the subject vertebrate, and (d) determining that said subject vertebrate has every type of poorer prognosis . . . , wherein MN/CA IX protein is encoded by just any nucleotide sequences that hybridize under stringent hybridization conditions of 50% formamide at 42 degrees C to any complement of SEQ ID NO:1's coding region or degenerate sequences thereof.

[Office Action, in paragraph bridging pages 10-11; emphasis in the original.]

The Office Action concludes at page 17: "In view of the teachings above and lack of guidance, working examples and or exemplification in the specification, it would require undue experimentation by one of skill in the art to determine with any predictability, that the method would function as claimed." Applicants respectfully traverse, submitting that for enablement, the burden of proof is upon the Examiner to challenge a presumptively enabling disclosure [MPEP § 2164.04], and no evidence has been presented as to why the methods would not work as claimed.

Applicants respectfully submit that once a pattern of prognosis for a genus of diseases is established, it is conventional knowledge to apply those patterns for those diseases, in the absence of evidence to the contrary. The standard for enablement is not absolute certainty, but whether "it is more likely than not true"; and case law supports the view that some inoperative embodiments are permissible.

An "applicant does not have to provide evidence sufficient to establish that an asserted utility is true 'beyond a reasonable doubt.' In re Irons, 340 F.2d 974, 978, 144 USPQ 351, 354 (CCPA 1965). Instead, evidence will be sufficient if, considered as a whole, it leads a person of ordinary skill in the art to conclude that the asserted utility **is more likely than not true**." [MPEP § 2164.07.]

In re Marzocchi

The Federal Circuit quoted from In re Marzocchi, 169 USPQ 367, 369 (CCPA 1971) in In re Brana, 34 USPQ2d 1437 at 1441 (Fed. Cir. 1995) as follows:

> [A] specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented *must* be taken as in compliance with the enabling requirement of the first paragraph of § 112 *unless* there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support.

[Emphasis in the original.]

MPEP § 2164.04 entitled "Burden on the Examiner Under the Enablement Requirement" directs that the initial burden of proof to challenge a presumptively enabling disclosure is upon the Examiner. The patent case law, as well as the MPEP, makes clear that in accordance with case law, statements in a patent specification relied upon for enabling support that correspond in scope to a claimed invention "*must* be taken as in compliance with the enabling requirement of the first paragraph of § 112 *unless* there is reason to doubt the objective truth of" those statements. [In re Marzocchi, supra; italicized emphasis in the original; underlined emphasis added.] Applicants respectfully submit that there is no reason to doubt the

objective truth of statements relied upon for enabling support in the Specification for the claimed invention.

Applicants respectfully point out that at the time of filing an application, an applicant need not have any examples. An invention may be constructively reduced to practice by filing an application with no working examples at all or with paper examples. As the Federal Circuit has stated:

> The first paragraph of § 112 requires nothing more than objective enablement. *In re Marzocchi*, . . . , 169 USPQ 367, 369 (CCPA 1971). How such a teaching is set forth either by the use of illustrative examples or by broad terminology, is irrelevant.

[In re Vaeck, 20 USPQ2d 1438 at 1445 (Fed. Cir. 1991); emphasis added.]

As discussed below, the Specification teaches how the claimed methods can be used for the range of diseases, tissue samples, types of prognosis, and variants of MN/CA IX proteins/polypeptides, corresponding in scope with the breadth of the claims.

1. Range of Preneoplastic/Neoplastic Diseases

The Office Action states at page 15 that "absent evidence of the polypeptide's expression in a particular tissue including the correlation to a diseased state, one of skill in the art would not be able to predictably use the polypeptide in any diagnostic or prognostic setting without undue experimentation." As support, the Office Action cites Tockman et al., Cancer Res., 52: 2711s-2718s (1992), which teaches that "prior to the successful application of newly described markers, markers must be validated against acknowledged disease end points and the marker predictive value must be confirmed in prospective population trials. . . ." [Office Action, pages 14-15.]

Applicants respectfully submit that the Examiner is incorrect on several points: 1) the diagnostic expression patterns of CA IX have already been established for each of the preneoplastic/neoplastic diseases claimed in the instant invention; 2) CA IX is not just a tumor marker, but is also implicated in the progression of different tumor types; and 3) Tockman et al. 1992 is inapposite, as it relates to establishing

endpoints to identify whether a biomarker is diagnostically useful for a particular tumor, not whether or not an established tumor biomarker is useful prognostically. It is already well-established that CA IX plays an important role in the growth and survival of tumor cells in general [see, for example, Robertson et al., Cancer Res., 64(17): 6160-6165 (2004).] The Examiner has provided no evidence that would suggest that the claimed methods would not work in the manner exemplified in the Specification.

Tockman et al. 1992

As mentioned above, the Office Action cites Tockman et al. as teaching that "prior to the successful application of newly described markers, markers must be validated against acknowledged disease end points and the marker predictive value must be confirmed in prospective population trials. . . ." [Office Action, pages 14-15.] However, in the passage entitled "Biomarker Validation against Acknowledged Disease End Points" (cited at page 14 of the Office Action), the "end points" and the "predictive value" referred to by Tockman are strictly diagnostic, i.e., relate to whether or not subjects will contract the disease, not their later prognosis:

> These indices [sensitivity and specificity of a potential biomarker] are usually determined by applying the marker to specimens from one group of persons who have (or will develop) the disease and to specimens from another group who do not and then comparing the results . . .
>
> The essential element of the validation of an early detection marker is the ability to test the marker on clinical material obtained from subjects monitored in advance of clinical cancer and link those marker results with subsequent histological confirmation of disease.

[Tockman et al., 1992; at page 2714s, col.1; emphasis added.]

The instant invention is only directed to prognostic methods using MN/CA IX, which has already been well-established as a diagnostic marker for the diseases of the instant invention. The diseases subject to methods of the instant invention include "preneoplastic/neoplastic diseases of gastric mucosa, gallbladder, biliary ducts, ductal cells of duodenal glands, testis including ductular efferens and rete testis, ovary including surface coelomic epithelium and rete ovari, basal cells of

hair follicles, and central nervous system choroid plexus." [Instant specification, at page 9, lines 8-11.] It has already been established that decreased levels of MN/CA IX in those tissues are associated with cancer. [See Section IV. Written Description, supra]. Moreover, step (c) of Claim 1 compares the level of MN/CA IX protein/polypeptide in the subject's tissue sample with those found "in comparable samples taken from vertebrates afflicted by the same preneoplastic/neoplastic disease as the subject vertebrate . . ." [emphasis added], not from unaffected controls as in Tockman et al.

Moreover, based on MN/CA IX's unique correlation with the presence of hypoxia and the value of hypoxia in cancer prognosis in a broad range of tumors, the Specification teaches that renewed expression of MN/CA IX in tumor cells (after loss of initial normal expression) could signify hypoxia or tumor progression and corresponding poorer prognosis in diseases similar to gastric cancer. The Specification at page 42, lines 21-27 states:

> In summary, while the frequent loss of CA IX expression observed in gastric cancer may be an early event, the overexpression of CA IX at the invasion front of a subset of gastric cancers may lead to invasive growth and thereby contributes to the growth and progression of gastric cancer malignancy. **The inventors then conclude that preneoplastic/neoplastic diseases having similar CA IX expression patterns as that of gastric cancer would also be subject to the prognostic methods disclosed herein.**

[Emphasis added.]

MN/CA IX is unique in its association with tumor growth: "CA IX is not only a tumor marker but appears directly involved in the oncogenesis of different types of tumors." [Driessen et al., Ann Surg., 243(3): 334–340 (2006); at page 339 (available online at www.pubmedcentral.nih.gov/articlerender.fcgi?tool=pubmed&pubmedid= 16495697.] In the absence of any evidence to the contrary, MN/CA IX's expression patterns in preneoplastic/neoplastic diseases would be considered by those of skill in the art in view of the extensive literature on MN/CA IX to apply to a range of tissues with analogous normal MN/CA IX expression patterns.

2. **Samples of Preneoplastic/Neoplastic Tissues**

The Office Action indicates that the Specification is only enabling for a method prognostic for a patient with gastric cancer, comprising "detecting MN/CA 9 [sic] polypeptide in a sample comprising tissue from the invasion front of said gastric cancer. . . ." [Office Action, bottom of page 10; also see middle of page 13.] However, as noted above in Section IV [under Genus of Tissue Samples], the cancer samples in the Materials and Methods section and in the Examples are only identified as "gastric cancer" samples, not specifically as "invasion front" gastric cancer samples, although at least one of the samples in Example 3 is described as comprising an invasion front.

Also, at the bottom of page 15 the Examiner erroneously states: "Determining which preneoplastic/neoplastic diseases affect a tissue which tissue normally expresses MN/CA IX protein, but loses or has significantly reduced MN/CA IX expression upon carcinogenesis would require undue experimentation." As pointed out in the written description response [supra], conventional art referenced in the instant specification clearly teaches which cancers result in a decrease in MN/CA IX expression upon carcinogenesis.

Therefore, Applicants respectfully submit that the claims are enabled for any samples comprising preneoplastic/neoplastic tissue, which tissue normally expresses MN/CA IX but loses such expression upon carcinogenesis, and not just those samples that comprise the invasion front of that preneoplastic/neoplastic tissue, or just those samples that comprise the invasion front of gastric cancer.

3. **Types of Prognosis**

Also, the Examiner argues that the Specification is only enabled for prognostic methods for a patient with gastric cancer, comprising determining that "said patient has a prognosis of **shorter survival** than the average subject with gastric cancer . . ." [emphasis added], not "every type of poorer prognosis. . . ." [See Office Action, bottom of page 10, middle of page 11, bottom of page 13, and middle of page 15.] However, the Examiner has not provided any evidence that suggests that the

claimed prognostic methods would not work for any type of prognosis of preneoplastic/neoplastic diseases of tissues, where MN/CA IX is normally expressed but its expression is lost or diminished upon carcinogenesis.

4. MN/CA IX Protein/Polypeptide

The Examiner also contends that the Specification only teaches a method which is prognostic for a patient with cancer, comprising detecting MN/CA IX polypeptide, wherein MN/CA IX polypeptide is encoded by SEQ ID NO: 1 or sequences that differ from SEQ ID NO: 1 solely due to the degeneracy of the genetic code. [Office Action, bottom of page 13.]

In response, Applicants first respectfully point out that, due to the mutagenic nature of cancer, MN/CA IX proteins/polypeptides found in the preneoplastic/neoplastic tissues of patients may be encoded by nucleotide sequences that differ in sequence from SEQ ID NO: 1 or degenerate variants thereof. As pointed out in the instant Specification at page 31, lines 20-25:

> It can be appreciated that a protein or polypeptide produced by a neoplastic cell *in vivo* could be altered in sequence from that produced by a tumor cell in cell culture or by a transformed cell. Thus, MN proteins and/or polypeptides which have varying amino acid sequences including without limitation, amino acid substitutions, extensions, deletions, truncations and combinations thereof, fall within the scope of this invention.

Therefore, the instant claims should not be limited to detecting MN/CA IX proteins/polypeptides encoded by SEQ ID NO: 1 or sequences that differ from SEQ ID NO: 1 solely due to the degeneracy of the genetic code for reasons further elaborated in detail above.

As argued above in the response to the 35 USC § 112, ¶1 written description rejection, Applicants respectfully point out that Claim 1 has been amended to specify that the MN/CA IX protein/polypeptide "is specifically bound by the M75 monoclonal antibody that is secreted from the hybridoma VU-M75, which was deposited at the American Type Culture Collection under ATCC No. HB 11128." As the claimed methods are directed to detecting MN/CA IX proteins/polypeptides, and as

the M75 monoclonal antibody is highly specific for the MN/CA IX protein encoded by SEQ ID NO: 1 and was used for the exemplary immunohistochemical assays in the Examples of the instant specification, there is sufficient enablement in the instant claims with respect to the MN/CA IX protein/polypeptide to which the claims refer.

Enablement Conclusion

Applicants respectfully remind the Examiner that MPEP § 2164.04 entitled "Burden on the Examiner Under the Enablement Requirement" directs that the initial burden of proof to challenge a presumptively enabling disclosure is upon the Examiner. The patent case law, as well as the MPEP, makes clear that in accordance with case law, statements in a patent specification relied upon for enabling support that correspond in scope to a claimed invention "*must* be taken as in compliance with the enabling requirement of the first paragraph of § 112 *unless* there is reason to doubt the objective truth of" those statements. [In re Marzocchi, 169 USPQ 367, 369 (CCPA 1971); italicized emphasis in the original; underlined emphasis added.]

Applicants respectfully conclude that the Office Action has provided insufficient evidence of "reason to doubt" the objective truth of statements relied upon for enabling support in the Specification for the claimed invention, and that the initial burden of proof has not been carried. However, Applicants respectfully further conclude that even if that **hypothetical** initial burden had been shifted to the Applicants, that the Applicants would have dispelled that **hypothetical** burden by the above explanations and remarks.

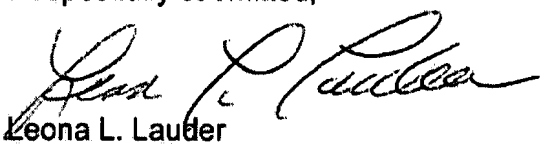
Applicants finally conclude that the pending claims, particularly in view of the above amendments, have the sufficient support required by the enablement requirement, and respectfully request that the Examiner withdraw the instant 35 USC 112, first paragraph rejection.

CONCLUSION

Applicants respectfully conclude that the claims as amended are in condition for allowance, and earnestly request that the claims be promptly allowed. If for any reason the Examiner feels that a telephone conference would expedite the

prosecution of the subject application, the Examiner is invited to telephone the undersigned Attorney for Applicants at (415) 981-2034.

Respectfully submitted,



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1: Exp. Toxicol. Pathol. 2002 Nov;54(3):245-53.

Metallothionein in liver-biopsies from patients with different diseases.

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Metallothioneins (MT) are ubiquitous found in eukaryotic organism. MT have a potential for metal-storage and protect the cells against stress. On the genomic level, proinflammatory cytokines like interleukin-6 and transition metals like copper cause induction of MT. Therefore, an estimation of MT in liver-biopsies from patients with different diseases probably could help in identifying acute-phase reactions and processes which lead to increased copper. We investigated paraffin embedded liver biopsies from 170 patients and 13 control biopsies from cases of sudden death. Tissue was stained with a primary antibody against MT and a peroxidase technique was used to make results visible. A grading was performed using an immunoreactive score (IRS from 0-24) and by computer-aided measurement of the optical density (OD) of the stained tissue slides. Patients with cholestasis (IRS: 12.1 +/- 2.8, n = 11), autoimmune (10.6 +/- 3.1, n = 7) or inflammatory bowel diseases (IBD) (13.3 +/- 5.1, n = 4) and lymphoma (9.8 +/- 5.8, n = 21) showed marked increases in MT compared to the controls (5.2 +/- 2.8, n = 13). Patients with chronic hepatitis B or C or chronic alcoholic abuse had no elevation of MT. Furthermore, no correlation was found between histological damage and amount of MT except in cases of cholestasis, in which increased MT was observed. Results by OD confirmed the findings. In summary, we were able to demonstrate a clear increase of MT content in liver-biopsies in proinflammatory and cholestatic conditions. Marked elevation in patients with systemic diseases (like autoimmune-, IBD and lymphoma) seems to be best explained by an acute-phase induction of MT by proinflammatory cytokines. This could help in identifying these conditions in liver biopsies.

1: Anticancer Res. 1999 May-Jun;19(3B):2189-93.

Modified true-color computer-assisted image analysis versus subjective scoring of estrogen receptor expression in breast cancer: a comparison.

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BACKGROUND: Hormone receptor expression can be quantified by computerized image analysis in immunohistochemically stained specimens. When comparing semiquantitative scoring with computerized image analysis a review of the literature shows contradictory findings concerning the correlation of these two methods. Recent technical approaches have been developed with true-color computer-assisted image analysis facilitating new measurement designs. We performed a study with a new approach using the principle of semiquantitative assessment of hormone receptor content and measuring two different binary images (immunohistochemically stained nuclear area and total nuclear area). MATERIAL AND METHODS: Eighty formalin-fixed, paraffin-embedded and immunohistochemically stained breast cancer specimens were assessed for estrogen receptor expression by true color computer-assisted image analysis and by conventional light microscopy scoring according to Remmele (immunoreactive score (IRS) = staining intensity (SI) x percentage of positive cells (PP)). The results of both methods were correlated. RESULTS: Mean optical density (MOD) and subjective scoring of SI as well as stained nuclear area vs. total nuclear area and subjective scoring of stained cells (PP) showed a high correlation (Spearman correlation coefficient: 0.95, p-value: 0.0001 and 0.64, p-value: 0.0001, respectively). CONCLUSION: On the basis of this new technical approach our results confirm the correlation of semiquantitative hormone receptor scoring and quantitative computer-assisted image analysis. We believe that by automating electronic analysis in the near future we will be able to establish reliable observer-independent evaluation of immunohistochemical variables ensuing comparability in multi-center trials and cost efficiency.